		7		JC13 Rec'd PCT/PTO 1 6 MAR 2001
FORM:	PTO-139	((Modified) U.S. DEPARTMEN	FOR COMMERCEPATENTAND TRADEMARKOFF	CE ATTORNEY'SDOCKETNUMBER
			TO THE UNITED STATES	PU3514USW
		DESIGNATED/ELECTE	ED OFFICE (DO/EO/US)	U.S. APPLICATIONNO. (IF KNOWN, SEE 37 CFR
			NG UNDER 35 U.S.C. 371	09/787327
INTE		IONAIAPPLICATIONNO. PCT/EP99/06886	INTERNATIONAIFILINGDATE 17 September 1999	PRIORITYDATECLAIMED 18 September 1998
ANT	IVIR	NVENTION AL COMBINATIONS		
		T(S)FOR DO/EO/US Nathaniel A.; CONDREAY	, Lynn, D.; GRAY, Douglas, Fraser	r; RUBIN, Marc
Appli	cant l	erewith submits to the United St	ates Designated/Elected Office (DO/EO/U	S) the following items and other information:
1.	×	This is a FIRST submission of	items concerning a filing under 35 U.S.C.	. 371.
2.		This is a SECOND or SUBSEC	QUENT submission of items concerning	a filing under 35 U S C. 371.
3.	×	This is an express request to be examination until the expiration	gin national examination procedures (35) of the applicable time limit set in 35 U.S	U.S.C. 371(f)) at any time rather than delay i.C. 371(b) and PCT Articles 22 and 39(1).
4.	$\boxtimes$			by the 19th month from the earliest claimed priority date.
5.	$\boxtimes$	A copy of the International App	olication as filed (35 U S.C 371 (c) (2))	
l	a  is transmitted herewith (required only if not transmitted by the International Bureau).			
		b. 🖾 has been transmitted by the International Bureau.		
		c.   is not required, as the application was filed in the United States Receiving Office (RO/US).		
6.		A translation of the International Application into English (35 U.S.C. 371(c)(2))		
7.	8	A copy of the International Search Report (PCT/ISA/210).		
8.	X	_		
	a. are transmitted herewith (required only if not transmitted by the International Bureau)			
		b  have been transmitted by the International Bureau.  bave not been made; however, the time limit for making such amendments has NOT expired.		
			-	menoments has NOT expired.
9.		<ul> <li>d.          have not been made and will not be made.     </li> <li>A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(e)(3)).</li> </ul>		
10.	×	An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)). Condreay and Rubin		
11.	×	A copy of the International Preliminary Examination Report (PCT/IPEA/409).		
12.		A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).		
ı	tems :	3 to 20 below concern documen	nt(s) or information included:	
13.	$\boxtimes$	An Information Disclosure Statement under 37 CFR 1 97 and 1.98.		
14.		An assignment document for recording A separate cover sheet in compliance with 37 CFR 3 28 and 3.31 is included		
15.	$\bowtie$	A FIRST preliminary amendment		
16.		A SECOND or SUBSEQUENT preliminary amendment.		
17.		A substitute specification.		
18.		A change of power of attorney and/or address letter		
19:	×			
20.	Other items or information.			
		Copy of Form PCT/RO/101		
		Copy of PCT Publication C	over Sheet	

Page 1 of 2

PCTUS1/REVO

532 Rec'd PC ... 16 MAR 2001 U.S. APPLICATIONNO, (IF KNOWN, SEE 37 CFR INTERNATIONALAPPLICATIONNO ATTORNEY'SDOCKETNUMBER PCT/EP99/06886 PU3514USW 21. The following fccs are submitted CALCULATIONS PTOUSEONLY BASIC NATIONAL FEE ( 37 CFR 1.492 (a) (1) - (5)) : Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO . \$1,000.00 M International preliminary examination fee (37 CFR 1.482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO \$860.00 ☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1 445(a)(2)) paid to USPTO .... \$710.00 ☐ International preliminary examination fee paid to USPTO (37 CFR 1 482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) ... \$690.00 ☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) . . . . . . . . \$100.00 ENTER APPROPRIATE BASIC FEE AMOUNT = \$860.00 Surcharge of \$130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492 (e)). \$0.00 CLAIMS NUMBER FILED NUMBER EXTRA RATE Total claims 15 - 20 = \$18.00 \$0.00 Independent claims 4 - 3 = \$80.00 \$80.00 Multiple Dependent Claims (check if applicable) \$0.00 TOTAL OF ABOVE CALCULATIONS \$940.00 Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (check if applicable). \$0.00 SUBTOTAL \$940.00 Processing fee of \$130.00 for furnishing the English translation later than 20 months from the earliest claimed priority date (37 CFR 1.492 (f)) \$0.00 TOTAL NATIONAL FEE \$940.00 ee for recording the enclosed assignment (37 CFR 1.21(h)) The assignment must be ccompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable). \$0.00 TOTAL FEES ENCLOSED \$940.00 \_ ount to be: refunded s charged A check in the amount of to cover the above fees is enclosed Please charge my Deposit Account No 07-1392 in the amount of \$940.00 to cover the above fees A duplicate copy of this sheet is enclosed The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No 07-1392 A duplicate copy of this sheet is enclosed. NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition o revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status. SEND ALL CORRESPONDENCE TO: pren David J. Levy Glaxo Wellcome Inc. SIGNATURE Global Intllectual Property Dept. Five Moore Drive, PO Box 13398 Karen L. Prus Research Triangle Park, NC 27709 NAME Telephone: 919-483-2370 39,337 Fax: 919-483-7988 REGISTRATION NUMBER

Page 2 of 2

March 14 2001

DATE

# 532 Rec'd PCT/PTO 16 MAR 2001

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Nathaniel A. BROWN et al

International Application No.:

PCT/EP99/06886

Title:

International Filing Date: 17 September 1999 ANTIVIRAL COMBINATIONS

Commissioner of Patents Washington, D.C. 20231

## FIRST PRELIMINARY AMENDMENT

#### Dear Sir

The above identified application is being transmitted herewith for entry in the US National Phase under Chapter II of the PCT for the purpose of adding the priority information. Please amend the application as follows:

#### In the Abstract:

Please substitute the attached Abstract, which has been placed on a separate sheet of paper according to US practice, as required under 37 CFR 1.72(b)

#### In the Specification:

On the first line of the specification, after the Title, please add:

-- This application is filed pursuant to 35 U.S.C. §371 as a United States National Phase Application of International Application No. PCT/EP99/06886 filed 17 September 1999, which claims priority from GB9820420.9 filed 18 September 1998.--

#### In the Claims:

Please delete Claim 11 and Claims 16-21.

Please amend the Claims as follows:

### Clean Copy of Amended Claims

Claim 1 (Amended in IPER) A combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent, bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight.

Claim 2. A combination according to claim 1 wherein the ratio is in the range 25:1 to 15:1 by weight of active ingredients.

Claim 3 (Amended here and in IPER) A combination according to claim 1 for use in medicine.

Claim 4 (Amended here and in IPER) A pharmaceutical formulation comprising a combination according to claim 1 in association with one or more pharmaceutically acceptable carriers therefor.

Claim 5 (Amended in IPER) A pharmaceutical formulation for use in the treatment of HBV comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or а pharmaceutically acceptable derivative thereof. and bis(pivalovloxymethyl)(9-[R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight.

Claim 6 (Amended here and IPER) A formulation according to claim 4 in unit dosage form.

Claim 7 (Amended here and IPER) A formulation according to claim 4 suitable for oral administration.

Claim 8 (Amended) A formulation according to claim 5 comprising between 25 to 150 mg of lamivudine and 5 to 60 mg adefovir dinivoxil

Claim 9 A formulation according to claim 8 comprising 100 mg of lamivudine and 10 mg adefovir dipivoxil.

Claim 10 A method for the treatment of a mammal, including a human, with an HBV infection comprising administration of a therapeutically effective amount of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof.

#### Delete Claim 11

Claim 12 (Amended) A method according to claim 10 wherein the combination is administered simultaneously.

Claim 13 (Amended) A method according to claim 10 wherein the combination is administered sequentially.

Claim 14 (Amended) A method according to claim 10 wherein the combination is administered as a single combined formulation.

Claim 15 (Amended) A method as claimed in claim 10 for the treatment of an HBV infection resistant to nucleoside and/or non-nucleoside inhibitors of the replication of the hepatitis B virus.

#### Delete Claims 16-21

Claim 22 (Amended in IPER) A patient pack comprising of at least one active ingredient selected from (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one, and bis(pivaloyloxymethyl)(9-[2-

(phosphonomethoxy)ethyl]adenine and an information insert containing directions on the use of both active ingredients together in combination.

#### REMARKS

Applicants have attached an abstract on a separate sheet of paper as required by US practice. Applicants have amended the specification for purposes of adding the priority information. The claims have been amended to place them in form appropriate to US practice and to reduce the filing fee by removing multiple dependency. Claims 1, 3, 4, and 5 have been amended to parallel the amended claims as indicated in the PCT International Preliminary Examination Report. Claims 11 and 16-21 have been deleted. It is respectfully submitted that the present application is in condition for allowance. An early consideration and notice of allowance are earnestly solicited.

Respectfully submitted;

Date: March 14, 2001

Karen L. PRUS

Attorney of Record, Reg. No 39,337

Glaxo Wellcome Inc. Global Intellectual Property Department Five Moore Drive, PO Box 13398 Research Triangle Park, NC 27709-3398 Telephone: 919-483-3323

Fax: 919-483-7988

#### ANTIVIRAL COMBINATIONS

#### Abstract

The present invention relates to therapeutic combinations comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one (lamivudine) and second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine, (PMEA or adefovir) and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine, (the oral prodrug of PMEA, adefovir dipivoxil) which have anti-hepatitis B virus (HBV) activity. The present invention is also concerned with pharmaceutical compositions containing said combinations and their use in the treatment of HBV infections including infections with HBV mutants bearing resistance to nucleoside and/or non-nucleoside inhibitors.

# Version With Markings to Show Changes Made to Claims

Claim 1 (Amended in IPER) A combination comprising (2R,cis)-4-amino-1-(2hvdroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent [selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or а pharmaceutically acceptable derivative thereof. and] bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1.3oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight.

Claim 2 A combination according to claim 1 wherein the ratio is in the range 25:1 to 15:1 by weight of active ingredients.

Claim 3 (Amended here and in IPER) A combination according to [any one of] claim[s] 1 [or 3] for use in medicine.

Claim 4 (Amended here and in IPER) A pharmaceutical formulation comprising a combination according to [any one of] claim[s] 1 [to 3] in association with one or more pharmaceutically acceptable carriers therefor.

Claim 5 (Amended in IPER) A pharmaceutical formulation for use in the treatment of HBV comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or pharmaceutically acceptable derivative thereof. and bis(pivaloyloxymethyl)(9-IR)-2-(phosphonomethoxy)ethyl]adenine pharmaceutically or а acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3oxathiolan-5-vl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight.

Claim 6. (Amended here and in IPER) A formulation according to claim[s] 4 [or 5] in unit dosage form.

Claim 7. (Amended here and in IPER) A formulation according to [any one of] claim[s] 5 [to 6] suitable for oral administration.

Claim 8. (Amended) A formulation according to [any one of] claim[s] 5 [to 7] comprising between 25 to 150 mg of lamivudine and 5 to 60 mg adefovir dipivoxil.

Claim 9. A formulation according to claim 8 comprising 100 mg of lamivudine and 10 mg adefovir dipivoxil.

Claim 10. A method for the treatment of a mammal, including a human, with an HBV infection comprising administration of a therapeutically effective amount of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof.

Claim 11 (Deleted)

Claim 12. (Amended) A method according to claim 10 [or claim 11] wherein the combination is administered simultaneously.

Claim 13. (Amended) A method according to claim 10 [or claim 11] wherein the combination is administered sequentially.

Claim 14. (Amended) A method according to claim 10 [or claim 11] wherein the combination is administered as a single combined formulation.

Claim 15. (Amended) A method as claimed in [any one of] claim[s] 10 [to 14] for the treatment of an HBV infection resistant to nucleoside and/or non-nucleoside inhibitors of the replication of the hepatitis B virus

Claim 16 (Deleted)

Claim 17 (Deleted)

Claim 18 (Deleted)

Claim 19 (Deleted)

Claim 20 (Deleted)

Claim 21 (Deleted)

Claim 22. (Amended in IPER) A patient pack comprising of at least one active ingredient selected from (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one, and bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine and an information insert containing directions on the use of both active ingredients together in combination.

30

5

10

PCT/EP99/06886 **39/**787327

## Antiviral Combinations

1

The present invention relates to therapeutic combinations comprising (2R,cis)-4amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one (lamivudine) and second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethylladenine. (PMEA or adefovir) and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine. oral prodrug of PMEA, adefovir dipivoxill. The present invention is also concerned with pharmaceutical compositions containing said combinations and their use in the treatment of HBV infections including infections with HBV mutants bearing resistance to nucleoside and/or non-nucleoside inhibitors of the replication of the hepatitis B virus.

Hepatitis B is a viral disease transmitted orally or parentally by contaminated material such as blood or blood products, contaminated needles, sexually, and vertically from infected or carrier mothers to their off-spring. In those areas of the world where the disease is common, vertical transmission at an early age results in a high proportion of infected individuals becoming chronic carriers of hepatitis B. An estimated 350 million people world-wide are chronically infected with hepatitis B and as many as 150 million may die from liver disease in the absence of intervention

Currently, the only established approach to treatment of hepatitis B is repeated injections of interferon, which may be associated with unpleasant side effects, and produces a long lasting response in only one third or less of those treated. Interferon is an immune modulator designed to boost the disease fighting ability of the immune system.

Lamivudine has been reported to be effective against HBV in a two year study, showing that most patients showed substantially reduced levels of viral replication with 52% maintaining undetectable levels of virus thorough to the end of the second year.

Adefovir has been reported to posses anti-HBV activity in vitro, and the oral prodrug of adefovir, adefovir dipivoxil, has been shown to be active against HBV replication in vivo and is currently in phase II clinical studies with patients who have chronic hepatitis B viral infection.

5

There has been a report that there is lack of cross-resistance to PMEA for Human hepatitis B DNA polymerase which expresses lamivudine codons, X. Xiong et al. (Hepatology Vol 26, No. 4, Pt. 2, 1997, Abstract No. 1211).

10

The use of combinations of the invention may give rise to equivalent antiviral effect with reduced toxicity, or an increase in drug efficacy because synergy between compounds occurs. Lower overall drug doses will also possibly reduce the frequency of occurrence of drug resistant variants of HBV.

3378755 34220

We have now found that lamivudine exhibits unexpected advantages when used in combination with adefovir. In particular the combinations shows a statistically significant synergistic anti-HBV effect. Early results have shown that the combination of lamivudine and adefovir dipivoxil also exhibits a synergistic anti-HBV-effect. It is a feature of this invention that the use of these drug combinations will provide synergistic antiviral effects, more complete viral suppression, viral suppression over longer periods, limit the emergence of drug resistant HBV mutants and allow better management of drug related toxicites. The use of these drug combinations may also result in a decrease of the number of, for example, tablets administered a day, therefore may increase patient compliance.

25

As will be appreciated by those skilled in the art, references herein to treatment extend to prophylaxis as well as to the treatment of established infections and symptoms.

30

Pharmaceutically acceptable salts of lamivudine, adefovir, or adefovir dipivoxil include those derived from pharmaceutically acceptable inorganic and organic acids. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene- p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic,

30

35

5

10

malonic, naphthalene-2-sulphonic and benzenesulphonic acids. Other acids such as oxalic acid, while not in themselves pharmaceutically acceptable may be useful in the preparation of salts useful as intermediates in obtaining compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g. magnesium), ammonium and  $NR_{+}$  (where R is  $C_{14}$  alkyl) salts.

Preferred esters of lamivudine, adefovir or adefovir dipivoxil are independently selected from the following group: (1) carboxvlic acid esters in which the noncarbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, methyl, n-propyl, t-butyl, or nbutyl), cycloalkyl, alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted by, for example, halogen,  $\mathbf{C}_{_{1.4}}$  alkyl, or  $\mathbf{C}_{_{1.4}}$  alkoxy), or amino; (2) sulphonate esters, such as alkyl- or aralkylsulphonyl (for example, methanesulphonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); and (4) phosphonate esters. In such esters, unless otherwise specified, any alkyl moiety present advantageously contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms. Any cycloalkyl moiety present in such esters advantageously contains from 3 to 6 carbon atoms. Any aryl moiety present in such esters advantageously comprises a phenyl group. Any reference to any of the above compounds also includes a reference to a physiologically acceptable salt thereof.

Particularly preferred esters are the mono-, di-, and triphosphate esters of lamivudine (which may be optionally blocked), or any other compound which upon administration to a human subject is capable of providing (directly or indirectly) said mono-, di-, or triphosphate ester.

Thus according to one aspect, the present invention provides a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second

bek

25

30

35

5

10

therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof

Preferably the second therapeutic agent is bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof

Combinations as described above may herein after be referred to as combinations according to the invention.

As used herein "pharmaceutically acceptable derivative" includes any pharmaceutically acceptable salt, ester or salt of such ester, of lamivudine, adefovir or adefovir dipivoxil or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) such a compound or an antivirally active metabolite or residue thereof.

The present invention further provides combinations according to the invention for use in therapy, particularly in the treatment of an HBV infection including infections resistant to nucleoside and/or non-nucleoside inhibitors of the replication of the hepatitis B virus.

According to another aspect, the present invention provides a method for the treatment of a mammal, including a human, suffering from an HBV infection comprising administration of a therapeutically effective amount of a combination according to the invention.

It will be appreciated that the compounds of the combination may be administered simultaneously, either in the same or different pharmaceutical composition, or sequentially. If there is sequential administration, the delay in administering the second active ingredient should not be such as to lose the benefit of a synergistic therapeutic effect of the combination of the active ingredients. It will also be understood that lamivudine, and adefovir dipivoxil, or the pharmaceutically acceptable derivatives thereof or adefovir or the

30

5

10

pharmaceutically acceptable derivatives thereof, whether presented simultaneously or sequentially, may be administered individually or in any combination thereof. Lamivudine, and adefovir dipivoxil or adefovir are preferably administered simultaneously or sequentially in separate pharmaceutical formulations, most preferably simultaneously.

Preferably the combination according to the invention is administered as a single combined formulation

The present invention also provides the use of lamivudine in the manufacture of a medicament for administration simultaneously or sequentially with adefovir or adefovir dipivoxil for the treatment of HBV infections. It will be appreciated that lamivudine, adefovir dipivoxil, or adefovir or any combination thereof (excluding adefovir and adefovir dipivoxil), may be used in the manufacture of the above medicament.

A further aspect of the invention is a combination according to the invention wherein the lamivudine and adefovir dipivoxil or adefovir are present in a synergistic ratio.

The synergistic effects of the combination of lamivudine and adefovir dipivoxil or adefovir or pharmaceutically acceptable derivatives thereof are seen over a ratio, for example, of 40:1 to 1:1 (by weight), preferably 25:1 to 15: 1 (by weight).

Conveniently each compound will be employed in the combination in an amount at which it exhibits anti-HBV activity when used alone.

The amount of a combination of lamivudine, adefovir or adefovir dipivoxil required to be effective as an anti-HBV agent will, of course, vary and is ultimately at the discretion of the medical practitioner. The factors to be considered include the route of administration and nature of the formulation, the animal's body weight, age and general condition and the nature and severity of the disease to be treated.

30

5

10

In general for lamivudine a suitable daily dose will be in the range of from about 0.1 to about 50 mg per kilogram body weight of the recipient per day, preferably in the range of 0.5 to 20 mg per kilogram body weight per day, most preferably in the range of 0.5 to 2 mg per kilogram body weight per day.

The compound is conveniently administered at a level of about 100 mg per day.

For adefovir dipivoxil a suitable daily dose will be in the range of from about 0.01 to about 10 mg per kilogram body weight of the recipient per day, preferably in the range of 0.01 to 1 mg per kilogram body weight per day, most preferably in the range of 0.01 to 0.05 mg per kilogram body weight per day.

Conveniently adefovir dipivoxil is administered at a level of about 10 mg per day.

For adefovir, a suitable daily dose will be in the range of from about 0.01 to about 10 mg per kilogram body weight of the recipient per day, preferably in the range of 0.01 to 1 mg per kilogram body weight per day, most preferably in the range of 0.01 to 0.05 mg per kilogram body weight per day.

Conveniently adefovir is administered at a level of about 10 mg per day.

Unless otherwise indicated all weights of active ingredients are calculated in terms of the drug per se. In the case of a pharmaceutically acceptable derivatives of lamivudine, adefovir dipivoxil or adefovir, or a solvate of any thereof the figures would be increased proportionately. The desired dose is preferably presented as two, three, four, five, six or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing from 1 to 1500 mg, preferably from 5 to 1000 mg, most preferably from 5 to 500 mg of active ingredient per unit dosage form. Alternatively, if the condition of the recipient so requires, the dose may be administered as a continuous infusion.

30

5

10

The components of the combination which may be referred to as active ingredients may be administered for therapy to an animal e.g. a mammal including a human in a conventional manner.

While it is possible for the active ingredients of the combination to be administered as the raw chemical it is preferable to present them as a pharmaceutical composition. Pharmaceutical compositions according to the present invention comprise a combination according to the invention in association with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formula and not deleterious to the recipient thereof. When the individual components of the combination are administered separately they are generally each presented as a pharmaceutical composition. The references hereinafter to compositions refer unless otherwise stated to compositions containing either the combination or a component thereof.

A combination of lamivudine and adefovir dipivoxil or adefovir or pharmaceutically acceptable derivatives thereof may conveniently be presented as a pharmaceutical composition with one or more pharmaceutically acceptable carrier thereof in a unitary dosage form. A convenient unitary dosage formulation contains the active ingredients in amounts of from 1 mg to 2 g each, for example, 2 mg to 200 mg such as 25 to 150 mg of lamivudine and 5 to 60 mg of adefovir or adefovir dipivoxil.

Pharmaceutical compositions may also be prescribed to the patient in "patient packs" containing the whole course of treatment in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacists divides a patients supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in traditional prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physicians instructions.

It will be understood that the administration of the combination of the invention by means of a single patient pack, or patients packs of each composition, within a package insert diverting the patient to the correct use of the invention is a desirable additional feature of this invention.

5

According to a further aspect of the invention there is provided a patient pack comprising at least one active ingredient of the combination according to the invention and an information insert containing directions on the use of the combination of the invention

10

According to another aspect the invention provides a double pack comprising in association for separate administration lamivudine and adefovir dipivoxil or adefovir or pharmaceutically acceptable derivatives thereof.

1675 /127 /112**8**0

Compositions include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods represent a further feature of the present invention and include the step of bringing into association the active ingredients with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

25

Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, caplets, cachets or tablets each containing a predetermined amount of the active ingredients; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

30

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in

5

10

a suitable machine the active ingredients in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycollate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Moulded tablets may be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredients therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Preferably the combinations according to the invention are administered orally.

Compositions suitable for topical administration in the mouth include lozenges comprising the active ingredients in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier. Compositions for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Topical administration may also be by means of a transdermal iontophoretic device.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by admixture of the active

25

30

5

10

combination with the softened or melted carrier(s) followed by chilling and shaping in moulds.

Formulations suitable for parenteral administration include aqueous and nonaqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents; and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or daily subdose of the active ingredients, as herein before recited, or an appropriate fraction thereof

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavouring agents.

The compounds of the combination of the present invention may be obtained in a conventional manner.

Methods for the preparation of lamivudine are described in International Patent Applications Numbers. WO91/17159, and WO 95/29174 incorporated herein by reference.

10

Methods for the preparation of adefovir are described in European Patent No. 206459, incorporated herein by reference.

Methods for the preparation of adefovir dipivoxil are described in European Patent No. 481214 incorporated herein by reference.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way. "Active ingredient" denotes lamivudine, adefovir dipivoxil or adefovir or multiples thereof or a physiologically functional derivative of any of the aforementioned compounds.

## Example 1: Tablet Formulation

The following formulations A, B and C are prepared by wet granulation of the ingredients with a solution of povidone, followed by addition of magnesium stearate and compression.

### Formulation A

	mg/tablet
Active Ingredient A	100
Active Ingredient B	30
Lactose B.P.	105
Povidone B.P.	7
Sodium Starch Glycollate	10
Magnesium Stearate	3
	255

## Formulation B

	mg/tablet
Active Ingredient A	100

Active Ingredient B	30
Lactose B.P.	75
Avicel PH 101	30
Povidone B.P.	7
Sodium Starch Glycollate	10
Magnesium Stearate	3
	255

# Formulation C

	mg/tablet
Active Ingredient A	100
Active Ingredient B	5
Lactose B.P.	100
Starch	25
Povidone	2
Magnesium Stearate	2
	234

The following formulations, D and E, are prepared by direct compression of the admixed ingredients. The lactose in formulation E is of the direct compression type (Dairy Crest - "Zeparox").

#### Formulation D

	mg/tablet
Active Ingredient A	100
Active Ingredient B	30
Pregelatinized Starch NF15	75
	205

Formu	
COIIIIU	

	mg/tablet
Active Ingredient A	100
Active Ingredient B	5
Lactose B.P.	70
Avicel	50
	225

## Formulation F (Controlled Release Formulation)

The formulation is prepared by wet granulation of the ingredients with a solution of povidone followed by the addition of magnesium stearate and compression.

	mg/tablet
Active Ingredient A	100
Active Ingredient B	30
Hydroxypropylmethylcellulose	28
(Methocel K4M Premium)	
Lactose B.P.	13
Povidone B.P.	7
Magnesium Stearate	2
	180

Drug release takes place over a period of about 6-8 hours and is complete after 12 hours.

## 10 Example 2: Capsule Formulations

## Formulation A

A capsule formulation is prepared by admixing the ingredients of formulation D in Example 1 above and filling into a two-part hard gelatin capsule. Formulation B (infra) is prepared in a similar manner.

#### Formulation B

	mg/capsule
Active Ingredient A	100
Active Ingredient B	5
Lactose B.P.	70
Sodium Starch Glycollate	10
Magnesium Stearate	1
	186

## Formulation C

	mg/capsule
Active Ingredient A	100
Active Ingredient B	30
Macrogel 4000 B.P.	170
	300

Capsules of formulation C are prepared by melting the Macrogel 4000 B.P., dispersing the active ingredient in the melt and filling the melt into a two-part hard gelatin capsule.

## Formulation D

	mg/capsule
Active Ingredient A	100
Active Ingredient B	5
Lecithin	50
Arachis Oil	50
	-
	205

ma

10

Capsules of formulation D are prepared by dispersing the active ingredient in the lecithin and arachis oil and filling the dispersion into soft, elastic gelatin capsules.

# 5 Formulation E (Controlled Release Capsule)

The following controlled release capsule formulation is prepared by extruding ingredients a, b, and c using an extruder, followed by spheronization of the extrudate and drying. The dried pellets are then coated with release-controlling membrane (d) and filled into a two-piece, hard gelatin capsule.

		mg/capsule
(a)	Active Ingredient A	100
	Active Ingredient B	30
(b)	Microcrystalline Cellulose	60
(c)	Lactose B.P.	60
(d)	Ethyl Cellulose	6
		256

### Example 3: Injectable Formulation

## Formulation A

	<u>s</u>
Active Ingredient A	100
Active Ingredient B	5
Hydrochloric Acid Solution 0.1 M or	
Sodium Hydroxide Solution 0.1 M q.s. to pH	4.0 to 7.0
Sterile water q.s. to	10 ml

The active ingredient is dissolved in most of the water (35°-40°C) and the pH adjusted to between 4.0 and 7.0 with the hydrochloric acid or the sodium

15

hydroxide as appropriate. The batch is then made up to volume with the water and filtered through a sterile micropore filter into a sterile 10 ml amber glass vial (type 1) and sealed with sterile closures and overseals.

Formulation B

Active Ingredient A 125 mg

Sterile, Pyrogen-free, pH 7 Phosphate

Buffer, q. s. to 25 ml

## Example 4: Intramuscular injection

Active Ingredient A	100 mg
Active Ingredient B	30 mg
Benzyl Alcohol	0.067 g
Glycofurol 75	0.94 g
Water for injection q.s. to	3.00 ml

The active ingredient is dissolved in the glycofurol. The benzyl alcohol is then added and dissolved, and water added to 3 ml. The mixture is then filtered through a sterile micropore filter and sealed in sterile 3 ml amber glass vials (type 1).

## Example 5: Syrup

Active Ingredient A	100 mg
Active Ingredient B	5 mg
Sorbitol Solution	0.6 g
Glycerol	0.85 g
Sodium Benzoate	0.0025 g
Flavour, Peach 17.42.3169	0.0125 ml
Purified Water q.s. to	5.00 ml

5

The active ingredient is dissolved in a mixture of the glycerol and most of the purified water. An aqueous solution of the sodium benzoate is then added to the solution, followed by addition of the sorbital solution and finally the flavour. The volume is made up with purified water and mixed well.

## Example 6: Suppository

	mg/capsule suppository
Active Ingredient A	100
Active Ingredient B	30
Hard Fat, B.P. (Witepsol H15 - Dynamit Nobel)	1770
	1900

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at  $45^{\circ}\text{C}$  maximum. The active ingredient is sifted through a  $200\mu\text{M}$  sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at  $45^{\circ}\text{C}$ , the remaining Witepsol H15 is added to the suspension and stirred to ensure a homogenous mix. The entire suspension is passed through a  $250\mu\text{m}$  stainless steel screen and, with continuous stirring, is allowed to cool to  $40^{\circ}\text{C}$ . At a temperature of  $38^{\circ}$  C to  $40^{\circ}\text{C}$ , 2.02 g of the mixture is filled into suitable, 2 ml plastic moulds. The suppositories are allowed to cool to room temperature.

## Example 7: Pessaries

	mg/pessary
Active Ingredient A	100
Active Ingredient B	5
Anhydrate Dextrose	160
Potato Starch	150
Magnesium Stearate	3
	418

COUNTY COUNTY

The above ingredients are mixed directly and pessaries prepared by direct compression of the resulting mixture.

30

35

Biological Data

## Example 8.

The human hepatoblastoma cell line (Hep-G2-2.2.15) which constitutively produces infectious HBV was seeded into 96 well microtiter plates at a density of 5 x 10³ cells per well. These cells were treated with a combination of lamivudine and PMEA on triplicate plates. Culture media containing drugs was replenished every other day for 9 days, at which time supernatants were collected and analyzed for HBV content.

The lamivudine/PMEA combination was tested twice in triplicate in matrix fashion. Experiment 1 utilised a lamivudine range of 100 nM to 0.14 nM (3-fold dilutions in columns), and PMEA, 9-[(R)-2-(phosphonomethoxy)ethylladenine (adefovir), at concentrations of 1 µM to 10 nM (3.16 fold dilutions in rows). Experiment 2 was performed with dilutions of Lamivudine ranging from 100nM to .045 nM (in 3-fold dilutions in columns), and a PMEA range of 5  $\mu$ M to 0.16 nM (3.16 fold dilutions in rows). Both drugs were diluted in a separate 96 well microtiter plate, and subsequently transferred onto plates containing the cell monolayers. Cells are grown in 150 µl RPMI 1640 supplemented with 2 mM L-Glutamine and 10% fetal bovine serum. Prior to transfer of drug, 120 µl of media was removed from the cells, leaving 30 µl on the monolayers to prevent drying. 90 µl of fresh media without drug was added, followed by the addition of 30 µl of 5X drug dilutions. Lamivudine and PMEA were each tested on their respective plates individually at the same concentrations. Data were normalised to values obtained with non-drug treated cells, and expressed as a percent of control for analysis.

The method used for detection of HBV has been previously described (*Jansen RW, Johnson LC, Averett, DR. High-Capacity in vitro* assessment of antihepatitis B virus compound selectivity by a virion-specific polymerase chain reaction assay. Antimicrob Agents Chem 1993; 37 (3): 441-447.). Briefly, HBV detection was performed by "capturing" virus from supernatants on Anti-HBsAg coated plates, washing, denaturing to release HBV DNA, performing PCR with biotinylated primers, streptavidin capture of biotinylated PCR products with concomitant probe hybridization, addition of substrate, and reading optical densities of the colorimetric reaction. Dilutions of a standardized HBV-containing

30

35

5

10

( )

supernatant were included on every plate, and HBV DNA concentrations of test wells were calculated from this HBV standard curve. The useful range of detection is at least .045 to 45 fg of HBV DNA, where 30 copies of the genome can be reliably detected. Samples were tested in conjunction with both positive (.448 fg/ul plasmid DNA) and negative (RPMI medium supplemented with 2 mM L-Glutamine and 10% Fetal calf serum) controls.

The average IC50 and standard error of the IC50s for the triplicate plates were calculated using SAS nonlinear regression to fit data to the Hill equation for each concentration response curve. When only a single determination of an IC50 for a particular dose combination could be made, the average of the standard errors from adiacent concentrations was used to estimate the standard error. Fractional inhibitory concentrations (FIC50) were calculated for each combination and plotted using the isobologram representation (Berenbaum, M.C. (1985) The Expected Effect of a Combination of Agents: the General Solution. J. Theor. Biol. 114, 413-431). To assess statistical significance of synergy or antagonism. an unpaired t-test was used to compare each sum of paired FIC50 values with the theoretical value of 1. P values less than 0.05 were considered statistically significant. Comparison of P values between experiments must be interpreted with great care, as the experiments utilized different test concentration ranges (or ranges useable by the isobologram method). In some cases not all concentrations tested could support calculation of an IC50, since response was inhibited to a greater extent than 50 percent of control for all doses.

Figure 1 shows a single isobologram, produced by combining the data from both experiments, showing a statistically significant synergism.

#### Example 9

The IC<sub>so</sub> for PMEA was determined against wild type (WT) and lamivudine resistant HBV transiently expressed in a cell culture system as described below. HepG2 cells were transiently transfected with plasmid containing the HBV genome that had the wild type sequence or contained the following lamivudine resistant mutations in the reverse transcriptase gene; M552I, M552V, L528M, L528MM552V. It was previously determined that only the M552I and L528MM555V mutations were observed in HBV infected patients that developed

30

35

5

10

resistance to lamivudine therapy although the individual M552V and L528M mutations partially contributed to the loss in sensitivity of lamiyudine against HBV replication in vitro (Allen Ml. Deslauriers M. Andrews CW. Tipples GA. Walters KA, Tyrrell DLJ, Brown N for the Lamiyudine Clinical Investigation Group, and Condreay LD. Identification and characterization of mutations in hepatitis B virus resistant to lamiyudine, HEPATOLOGY 1998: 27:1670-1677). HepG2 cells were seeded into 96-well Costar plates at 6300 cells per well in 150 ul of HepG2 media (Dulbecco's Modified Eagle Medium (DMEM), containing 10% fetal bovine serum) and were incubated overnight at 37°C. For each transfected well. 75 ng of plasmid DNA and 0.5 µl of lipofectamine (Gibco) were incubated together for 30 minutes at room temperature in 12.5 ul of OptiMem (Gibco) prior to addition of DNA/lipofectamine mixture to cells. Each well was rinsed with 150 ul of unsupplemented DMEM. The DNA/lipofectamine mixture was added to each well in a total volume of 150 µl of OptiMem media. The cells were incubated with the DNA/lipofectamine solution for 5 hours at 37°C. After incubation, 150 µl of DMEM containing 20% serum was added to each well and plates were incubated overnight at 37°C. The media was replaced with 150 µl of HepG2 media only or media containing PMEA.

2.2.15 cells were seeded into 96-well Costar plates at 2250 cells per well in 150 µl of complete media (RPMI media containing 10% fetal bovine serum) and were incubated overnight at 37°C. The media was replaced with 150 µl of complete media only or media containing the desired concentration of PMEA.

Transfected cells, as well as 2.2.15 stable HBV-producer cells, were treated with control drug-free media or media containing PMEA every other day (day 1, 3, and 5). Final concentrations of PMEA for cell treatment were used at 25, 5, 1, 0.2, 0.04  $\mu M$  (for WT plasmid transfected cultures and control 2.2.15 cells) or 125, 25, 5, 1, 0.2  $\mu M$  (for all mutant plasmid transfected cultures).

HBV DNA levels were quantitated from media harvested from cells on day 7 using the methods described in Jansen RW, Johnson LC, Averett, DR. High-Capacity in vitro assessment of anti-hepatitis B virus compound selectivity by a virion-specific polymerase chain reaction assay. Antimicrob Agents Chem 1993; 37 (3): 441-447. Further details are given in Example 8.

Cytotoxicity due to drug treatment was determined using the DNA stain Bisbenzimide (H33342 3HCl 4H<sub>2</sub>0; Calbiochem Company, La Jolla CA). After the media was harvested, the cells were fixed with 70% ethanol for 30 minutes.

5

10

Cells were rinsed once with serum-free media and incubated with the DNA stain Bisbenzimide (H33342 3HCl 4H2O; Calbiochem Corporation, La Jolla CA) at 33 ug/ml for 1 hour at 37°C in serum-free medium. Fluorescent values per well were determined with a Millipore Cytofluor 2350 fluorescent plate reader (excitation, 355 nm; emission, 460 nm; arbitrary units). CC<sub>so</sub> values of each compound (concentration of compound that is cytotoxic for 50% of cells) were determined from the percent toxicity of each concentration of compound compared to untreated (no drug) cells using the method described below. Concentration response curves generated from each construct in the transient transfection experiment were fit to the Hill equation (y =  $Vmax * (1 - (x^n)/(k^n +$  $x^n)))$  using non-linear regression to estimate the IC<sub>50</sub> (concentration of drug which inhibited HBV DNA production by 50%, compared to parallel drug-free cultures) and CC<sub>so</sub> of PMEA. The calculated IC<sub>so</sub> for each construct is shown with the 95% confidence bounds for the geometric means for n replicates. The program JMP (SAS, Cary NC) was used to perform student t-test evaluation of the data for determining statistically significant differences between treatment groups. The IC<sub>50</sub> of PMEA obtained against WT HBV produced by the 2.2.15 cells (0.43 uM) was also comparable to the IC<sub>so</sub> value (0.7 uM) using the same cell line. (Heijtink RA, De Wilde GA, Kruining J, Berk L, Balzarini J, De Clerca E. Holy A, Schalam SW. Inhibitory Effect of 9-(phosphonylmethoxyethyl)adenine(PMEA) on Human and Duck Hepatitis B Virus Infection. Antiviral Research 1993: 21 (2): 141-153).

**Table 1.** Comparison of IC<sub>50</sub>s of PMEA between WT HBV and HBV containing lamivudine resistant associated mutations *in vitro*.

HBV construct	IC <sub>so</sub> PMEA (95%CI)	x-fold change in IC <sub>50</sub>
2.2.15	0.43 uM (0.3 - 0.7 uM)	-
WT	0.53 uM (0.34 - 0.8 uM)	-
L528M/	1.3 uM (0.4 - 4.3 uM) <sup>+</sup>	2.5
M552V		
M552I	7.5 uM (1.8 - 32 uM)*	14
M552V	9.8 uM (3.1 - 31 uM)**	18
L528M	0.87 uM (0.4 - 2.0 uM)	1.6

- \* Statistically different IC $_{\rm 50}$ s of compound between mutant HBV and WT HBV, p < 0.05.
- \* IC<sub>50</sub>s are statistically different from each other, p < 0.05.
- 5~ For HepG2 cells, the cytotoxic IC  $_{50}$  for PMPA was greater than 125 uM, the cytotoxic IC  $_{50}$  for PMEA varied between 25 to 40 uM.

DOYSTAT CHENNY

25

30

1

## Claims

U3514-PCT

- 1. A combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent, bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight.
- 2. A combination according to claim 1 wherein the ratio is in the range 25:1 to 15:1 by weight of active ingredients.
- 3. A combination according to any one of claims 1 to 3 for use in medicine.
- 4. A pharmaceutical formulation comprising a combination according to any one of claims 1 to 3 in association with one or more pharmaceutically acceptable carriers therefor.
- 5. A pharmaceutical formulation for use in the treatement of HBV comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight.
- 6. A formulation according to claims 4 or 5 in unit dosage form.
- 7. A formulation according to any one of claims 4 to 6 suitable for oral administration.

35

5

25 August 2000

- 8. A formulation according to any one of claims 5 to 7 comprising between 25 to 150 mg of lamivudine and 5 to 60 mg adefovir dipivoxil.
- A formulation according to claim 8 comprising 100 mg of larnivudine and 10 mg adefovir dipivoxii.
- 10. A method for the treatment of a mammal, including a human, with an HBV infection comprising administration of a therapeutically effective amount of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof.
- 11. A method as claimed in claim 10 wherein the combination is as claimed in any of claims 1 to 3,
- 12. A method according to claim 10 or claim 11 wherein the combination is administered simultaneously.
- 13. A method according to claim 10 or claim 11 wherein the combination is administered sequentially.
- 25 14. A method according to claim 10 or claim 11 wherein the combination is administered as a single combined formulation.
  - 15. A method as claimed in any one of claims 10 to 14 for the treatment of an HBV infection resistant to nucleoside and/or non-nucleoside inhibitors of the replication of the hepatitis B virus
  - 16. Use of (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one in the manufacture of a medicament for administration either simultaneously or sequentially with bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine, for the treatment of an HBV infection.

PU3514-PCT

25 August 2000

3

- 17. Use of bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine in the manufacture of a medicament for administration either simultaneously or sequentially with (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pvrimidin-2-one for the treatment of an HBV infection.
- 18. Use of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl)adenine or a pharmaceutically acceptable derivative thereof for the treatment of an HBV infection.
- 19. Use of a combination as claimed in any one of claims 1 to 3 for the treatment of an HBV infection.
- 20. Use of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiclan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from either (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, or bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight, for the treatment of an HBV infection resistant to nucleoside and/or nonnucleoside inhibitor.
- 21. Use of a combination as claimed in any one of claims 1 to 3 for the treatment of an HBV infection resistant to nucleoside and/or nonnucleoside inhibitor of the replication of the hepatitis B virus.
- 22. A patient pack comprising of at least one active ingredient selected from (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one, and bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine and an information insert containing directions on the use of both active ingredients together in combination.

30

35

25

5

10

09/27/10/2010/10/2011

FIG. 1 COMBINATION ISOBOLOGRAM 1.2 LAMIVUDINE VS ADEFOVIR EXPT'L - ADDITIVE 1 0.8 FIC (ADEFOVIR) 0.6 0.4 0.2 0 0.2 0 0.4 0.6 0.8 1.2 FIC (LAMIVUDINE) **NET SUM** -3.102370207 SE 1.29895894 -2.388351257 t AV DEV -0.141016828

0.013449974

P (DEV)

		DECLA	RATION FOR "371" AI	PPLICATION	
	BINED DECLAR LICATION WITH			R DESIGN PATENT	ATTORNEY'S DOCKET PU3514USW
AIII	First Names Inventor. BROWN, Nathaniel A.				
	laration submitted with initial	-			Complete if known: App No.:
( )Decla	tration submitted after initial f	iling (surcharge re	quired 37CFR1.16(e))		Filing Date
					Group Art Unit:
	As below named	inventor. I here	by declare that:		
	My residence, post office	address and citiz	enship are as stated belo	ow next to my name.	
				te is listed below) or an original, aimed and for which a patent is s	
0	the specification of which	(check only one	ANTIVIRAL COME item below):	BINATIONS	
09787387,042001	[ ] jis attached hereto.  OR  OR  [x] was filed on 17 September 1999 as United States application Serial No or PCT International  Application Number PCT/EF99/06886 filed and was amended on (MM/DD/YYYY) (if applicable)  I hereby state that I have reviewed and understand the contents of the above-identified s <sub>i</sub> ecification, including the claims, as amended by any amendment specifically referred to above.  I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.  I hereby claim foreign priority benefits under 35, U.S.C. §119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for				
	r Foreign Application		IMS UNDER 35 U.S.C Country	Foreign Filing Date	PRIORITY
ĺ	Number (s)			(MM/DD/YYYY))	CLAIMED
1. 9820 2.	0420.9		GB	09/18 /1998	X
3.					
4.					
5.	claim the benefit under T	itle 35 United S	tates Code 8119(a) of as	y United States provisional appl	ication(s) listed below
1 Mereo	Application No.	nic 55, Officer 5		e (MM/DD/YYYY)	ication(s) fisied below.
1.					
2.					
4.					

60
Z.
1
100
1
141
N
1
*
12
IU
2004
Sea

COL	COMBINED DECLARATION FOR UTILITY OF DESIGN  ATTORNEYS BOCKET NUMBER DISCLASSES BOCKET NUMBER DISCLASSES						
COM	IDINED DE	CLARATION FOR UT	TELL OF DESIGN	PU3514USW			
PAT	ENT APPLI	CATION WITH POWI	ER OF ATTORNEY Conti-	nued			
	FULL NAME	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL			
2	OF INVENTOR	RUBIN	Marc				
1	INVENTOR'S						
1	SIGNATURE .						
0	RESIDENCE &	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP			
1	CITIZENSHIP	Chapel Hill	NC	US			
1	POST OFFICE	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY			
4	ADDRESS	Glaxo Wellcome Inc.	Research Triangle Park	NC 27709, US			
1		Five Moore Drive, PO Box	1				
1	I	13398	1				

		DECLA	RATION FOR "3/	I" APPLICATION			
	BINED DECLA ICATION WIT			OR DESIGN PATENT VEY	PU3514 First Nam	EY'S DOCKET 4USW es Inventor: Nathaniel A.	
	laration submitted with initi ration submitted after initia	-	2quired 37CFR1.16(e			te if known: .: late	
	As below name	ed inventor. I here	by declare that:			}	
	My residence, post offic	e address and citi	zenship are as stated	d below next to my name.			
				name is listed below) or an origina is claimed and for which a patent is			
0	the specification of which	ch (check only one		OMBINATIONS			
COPRIDER CHERRY	[ ] is attached hereto.  OR [ x ] was filed on 17 September 1999 as United States application Serial No.  or PCT International						
	Application Number PCT/EP99/06886filed and was amended on (MM/DD/YYYY) (if applicable)						
0	1 hereby state that I have as amended by any ame			ts of the above-identified specificat	ion, including	the claims,	
nu m	I acknowledge the duty	to disclose inform	ation which is mate	rial to patentability as defined in 37	CFR §1.56.		
	I hereby claim foreign priority benefits under 35, U.S.C. §119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed:						
	FOREIGN AND ANY						
Prio	Foreign Application Number (s)		Country	Foreign Filing Dat (MM/DD/YYYY)		PRIORITY CLAIMED	
1. 9820			GB	09/18 /1998		X	
2.							
3. 4.		ļ					
5.							
	claim the benefit under	Title 35, United S	tates Code §119(e)	of any United States provisional ap	plication(s) li	sted below:	
	Application No.			Date (MM/DD/YYYY)			
2.							
3.					-		
4.					+		

-						
	IBINED DECLAR			R DESIGN PATENT	PU3514U	ISW
MILION WITH TO WER OF MITORIES					First Names I BROWN, Na	
					Complete	if known
(X) Dec	daration submitted with initial	filing or		•	App No.:	у кноши:
( )Decl	aration submitted after initial f	iling (surcharge r	equired 37CFR1.16(e))		Filing Date	
					Tinig Date	
					Group Art	Unit:
	As below named	inventor. I her	eby declare that:		<del></del>	
	My residence, post office	address and citi	zenship are as stated bel-	ow next to my name.		
				e is listed below) or an original, simed and for which a patent is s		
			ANTIVIRAL COME	INATIONS		
Cl	the specification of which	(check only on				
	[ ]is attached hereto. OR					
CO CO	[ x ] was filed on 17 Sept	tember 1999 as	United States applicatio	n Serial No or	PCT Internat	tional
lui Mi	Application Number PC	T/EP99/06886f	iled_and was amended or	(MM/DD/YYYY)	(if	applicable)
9787327.042801	I hereby state that I have a as amended by any amend			the above-identified specification	on, including	the claims,
74	I acknowledge the duty to	disclose inform	nation which is material	o patentability as defined in 37	CFR §1.56.	
O	or inventor's certificate or	r 365(a) of any I	PCT international applica	(d) or §365(b) of any foreign ap tion which designated at least or	ne country of	her than the
- April				low, by checking the box, any fi tion having a filing date before t		
	which priority is claimed:		C i international applica	tion naving a tiling date before t	nat of the app	ncation on
PRIO	R FOREIGN AND ANY P	RIORITY CL	AIMS UNDER 35 U.S.C	. 119:		
Pric	r Foreign Application		Country	Foreign Filing Date		PRIORITY
1. 982	Number (s)		GB	(MM/DD/YYYY)) 09/18 /1998		CLAIMED X
2.	0420.9			09/16/1996		
3.						
4.						
5.				L		
1 hereb	Application No.	itle 35, United S		y United States provisional app (MM/DD/YYYY)	heation(s) hs	ted below:
1.	друпсацоп No.	<del></del>	rung Dat	(MINDD/IIII)		
2.						
3.						
4.						
5.			I		1	

# COMBINED DECLARATION FOR UTILITY OF DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued

ATTORNEY'S DOCKET NUMBER PU3514USW

I hereby claim the benefit under 35, U.S.C. § 120 of any United States application or § 365(c) of any PCT international application designating the United States of America that is listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the distributions in material to patentiability as defined in 37 C.F.R. § 156 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

DDIO	DIIC DADENCE	A DDI TO LETTON	n.					
FKIO	K U.S. PARENT	APPLICATION or F	CT PARENT	APPLICAT	ON			
TIS	S. Parent Application of	IN DCT Downst	n				TUS (Check	
	Number	i FC1 Farent	Parent Filing (MM/DD/YY		PATENTI	D	PENDING	ABANDONED
POWE	R OF ATTORNEY:	As a named inventor, I here k Office connected therewith	by appoint the follo	owing attorney(s	) and/or agent(s) to	prosecute t	hts application	and transact all busines
Ch Ka Ro	avid J. Levy narles E. Dadswell aren L. Prus obert H. Brink izabeth Selby	Reg No 27,655 Reg No 35,851 Reg No 39,337 Reg. No. 36,094 Reg. No. 38,298	Frank P Christon	P. Riek a C. Bennett P. Grassler pher P. Rogers ann Morgan	Reg. No. 39,009 Reg. No. 37,092 Reg. No. 31,164 Reg. No. 36,334 Reg. No. 38,181	Bon: John	nie L Deppenb L. Lemanowic	rock Reg No. 28,209 z Reg. No. 37,380
	Correspondence to					Dire	ct Telephone C	alls to:
David J. Levy, Patent Counsel Global Intellectual Property Department Glaxo Wellcome Inc. Five Moore Drive. PO Box 13398 Research Triangle Park, NC 27709				23347 PATENT TRADEMARK OFFICE			Karen L. Prus 919-483-2192	
	willful false etat	tements may jeor!:-	mishable by fine	or imprison	ment or both	ndor 10 t	TCC 1001	uade on informatio villful false and that such
	FULL NAME OF INVENTOR	tements may jeopardize	the validity of	or imprison	ment, or both, on on or any pater	inder 18 t t issuing t	TCC 1001	and that such
2)	FULL NAME OF INVENTOR INVENTOR'S SIGNATURE	FAMILY NAME BROWN	the validity of	the applicati	ment, or both, on on or any pater	t issuing t	J.S.C. 1001, hereon.	and that such
P.J	FULL NAME OF INVENTOR INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP	FAMILY NAME BROWN CITY Cambridge	the validity of	the applicati TRST GIVEN NAM Nathaniel STATE OR FOR	ment, or both, ton or any pater	seco	J.S.C. 1001, hereon.	and that such
FROD	FULL NAME OF INVENTOR INVENTOR'S SIGNATURE RESIDENCE &	FAMILY NAME BROWN  CITY Cambridge POST OFFICE ADDRESS Glaxo Wellcome In	c.	the application of the applicati	ment, or both, i on or any pater	secce A.	J.S.C. 1001, thereon.	and that such
	FULL NAME FULL NAME FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS FULL NAME	FAMILY NAME	c.	the application of the applicati	ment, or both, to on or any pater  E  EIGN COUNTRY  Triangle Park	secce A.  Secce A.  Court US  STAT  NC	J.S.C. 1001, hereon.  OND GIVEN NAME  S   DC    VIEW OF CITIZEN  E & ZIP CODECC  27709, US	and that such
+2000	FULL NAME OF INVENTOR INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS	EMILLY NAME BROWN  CITY Cambridge POSTOFFICE ADDRESS Glaxo Wellcome In Five Moore Drive, J	c.	e or imprison the applicati TRST GIVEN NAM Nathaniel  STATE OR FOR MA E CITY Research	ment, or both, to on or any pater  E  EIGN COUNTRY  Triangle Park	secce A.  Secce A.  Court US  STAT  NC	J.S.C. 1001, thereon.  INDIGIVEN NAME  A DO DE COLUMN TO THE STREET OF CITIZEN  E & ZIP CODE/CO	and that such
	FULL NAME OF INVENTOR'S INVENTOR'S ISIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS FULL NAME OF INVENTOR'S SIGNATURE INVENTOR'S SIGNATURE	FAMILY NAME BROWN CITY CITY CAMPING CONDITION FAMILY NAME FA	c.	THE STATE OR FOR MA PARTY CITY Research  FIRST GIVEN N. L. YNN  FIRST GIVEN N. L. YNN  LYNN	ment, or both, to on or any pater  E  LEIGN COUNTRY  Triangle Park	SECO D.	J.S.C. 1001, hereon.  OND GIVEN NAME  STORY OF CITIZEN  E & ZIP CODECC  27709, US  ND GIVEN NAME	and that such  ANTHAL  OOO / ISSUIP  UNITRY
1	FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS  FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP RESIDENCE & CITIZENSHIP	FAMILY NAME BROWN CITY CITY CAMPING COMPTICE ADDRESS GGIAV WELCOME THE MORE AVECTOR FAMILY NAME CONDREAY CITY CITY RABILET AND THE ADDRESS CONDREAY CITY RABLET AND THE ADDRESS CONDREAY	c.	or imprison the applicati the applicati Nathaniel  STATE OR FOR MA TOTAL Research FIRST GIVEN N Lynn  STATE OR FOR NC	ment, or both, to on or any pater  E  EIGN COUNTRY  Triangle Park	seco A.  Seco A.  Seco A.  Seco A.  Seco A.  Seco Court NC  Seco D.	J.S.C. 1001, hereon.  S.J. O.J.  STRY OF CITIZEN  E. & ZIP CODECC 27709, US  ND GIVEN NAME	and that such  ONTHAL  ODO / SISIIP  ONTHAL  ONTHAL
1	FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & RESIDENCE ADDRESS FULL NAME OF INVENTOR INVENTOR INVENTOR SIGNATURE RESIDENCE SIGNATURE RESIDENCE & RESI	EMERICAN THE PROPRIETA OF THE PROPRIETA	e the validity of	STATE OR FOR NC	ment, or both, to on or any pater  E  LEIGN COUNTRY  Triangle Park	seco A.  Seco D.  SECO D.	J.S.C. 1001, hereon.  OND GIVEN NAME  STORY OF CITIZEN  E & ZIP CODECC  27709, US  ND GIVEN NAME	and that such  ONTHAL  ODO / SSIIP  ONTHAL  ONTHAL
1 2 0	FULL NAME OF INVENTOR INVENTOR'S INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS FULL NAME FULL NAME FULL NAME FULL NAME FULL NAME FULL NAME	PAMILY NAME  BROWN  A CITY  CITY  CAMPRICE ADDRESS  CITY  CONDREAS  CITY  Raleigh  POST OFFICE ADDRESS  CITY  Raleigh  FOST OFFICE ADDRESS  CITY  CITY  CITY  CITY  CONDREAY  CITY  CITY  CITY  CITY  CITY  CONDREAS  CITY  CI	c. PO Box 13398	STATE OR FOR NC	ment, or both, to no or any pater  EEGS COUNTRY  Triangle Park  AME  EIGN COUNTRY  Friangle Park	SECO A.  SECO B.  SECO B.  STAT NC  SECO D.	J.S.C. 1001, hereon.  SIND GIVEN NAME  SIND OF CITIZEN  STRY OF CITIZEN  E & ZIP CODECC  27709, US  SITE OF CITIZEN  E & ZIP CODECC  27709, US	and that such  ANTIAL  OOO   SSHIP  ANTIAL  SHIP  UNITRY
1 2	FULL NAME OF INVENTOR'S INVENTOR'S INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS  FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS  FULL NAME OF INVENTOR'S SIGNATURE INVENTOR'S SIGNATURE INVENTOR'S INVENTOR'S INVENTOR'S INVENTOR'S INVENTOR'S INVENTOR'S	DAMIY RANDS BROWN	c. PO Box 13398	e or imprison the applicati the application of th	ment, or both, to no or any pater  EEGS COUNTRY  Triangle Park  AME  EIGN COUNTRY  Friangle Park	SECO A.  SECO B.  SECO B.  STAT NC  SECO D.  SEC	J.S.C. 1001, thereon.  IND GIVEN NAME  J. J	and that such  CINITIAL  OOO / SSHIP  UNITIAL  SHIP  UNITIAL
1 2 0	FULL NAME OF INVENTOR SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS  FULL NAME OF INVENTOR'S SIGNATURE FULL NAME OF INVENTOR'S SIGNATURE ENSIDENCE & CITIZENSHIP POST OFFICE ADDRESS  FULL NAME OF INVENTOR'S	PAMILY NAME  BROWN  A CITY  CITY  CAMPRICE ADDRESS  CITY  CONDREAS  CITY  Raleigh  POST OFFICE ADDRESS  CITY  Raleigh  FOST OFFICE ADDRESS  CITY  CITY  CITY  CITY  CONDREAY  CITY  CITY  CITY  CITY  CITY  CONDREAS  CITY  CI	c. PO Box 13398  F. C.	Or imprison the applicati THEST GIVEN NAM NATHANIEL  STATE OR FOR MA PICTY RESEARCH  STATE OR FOR MA PICTY RESEARCH  STATE OR FOR NC GIVEN NAM OOUGIAS	ment, or both, to no or any pater  EXECUTED TO THE TENER OF THE TENER	under 18 Ut issuing to A. A. A. COUNTY US STAT NC SECO Fra:	J.S.C. 1001, hereon.  3 20  NIRE OF CITIZEN  E & ZIP CODECC  27709, US  ND GIVEN NAME  HIRV OF CITIZEN  E & ZIP CODECC  27709, US  ND GIVEN NAME  ND GIVEN NAME  E & ZIP CODECC  E & ZIP CODEC	and that such  CINITIAL  OOO  INSIDE  VINITIAL  SHIP  UNITRY  UNITIAL
1 2 2	FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS  FULL NAME OF INVENTOR'S SIGNATURE FULL NAME OF INVENTOR'S SIGNATURE ADDRESS  FULL NAME OF INVENTOR'S FULL NAME OF INVENTOR'S FULL NAME OF INVENTOR'S FULL NAME OF INVENTOR'S SIGNATURE FULL NAME OF INVENTOR'S SIGNATURE SIGNATURE FULL NAME OF INVENTOR'S SIGNATURE SIGNATURE	DAMILY NAME  CITY Cambridge CONDRESS Glaxo Wellcome In Five Moore Drive, I FAMILY NAME GRAY  CHY Raleigh FOST OFFICE ADDRESS Glaxo Wellcome In Five Moore Drive, I FAMILY NAME GRAY  GRAY  GRAY  GRAY	c. PO Box 13398  F. C. PO Box 13398	Or imprison the application of t	ment, or both, to no or any pater  EXECUTED TO THE TENER OF THE TENER	Inder 18 t t issuing t t issuing t t issuing t A. A. A. A. COURT OF THE COURT OF TH	J.S.C. 1001, thereon.  IND GIVEN NAME  J. J	AND THAT I SHIP

C.
Ü
1
00
1
12.5
(4)
3
20
1000
F
19
0
1940
1

COM PAT	ENT APPLI		TILITY or DESIGN ER OF ATTORNEY Cont	ATTORNEY'S DOCKET NUMBER PU3514USW
2	FULL NAME OF INVENTOR	RUBIN	FIRST GIVEN NAME Marc	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE			
0	RESIDENCE & CITIZENSHIP	Chapel Hill	NC STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP US
4	POST OFFICE ADDRESS	Glaxo Wellcome Inc.	Research Triangle Park	STATE & ZIP CODE/COUNTRY NC 27709, US
		Five Moore Drive, PO Box 13398		,

# COMBINED DECLARATEN FOR UTILITY OF DESIGNATION WITH POWER OF ATTORNEY Continued

ATTORNEY'S DOCKET NUMBER
PU3514USW

I hereby claim the b-mefit under 35, U.S.C. §120 of any United States application or §365(c) of any PCT international application designating the United States of America mat is listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States of PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentiability as defined in 37 CF R. §1.56 which became available between the filing date of the prior application(s) and the national or PCT international Gline date. 6(in emplication:

		ling date of this applic					
PRIO	R U.S. PARENT	APPLICATION	or PCT PARE	NT APPLICATI	ON	CTATTIC (CL. 1	
115	Parent Application or	PC'T Parent	Darent H	iling Date	PATENTED	STATUS (Check	ABANDONED
0.3	Number Number	retraient		D/YYYY)	FATENTED	FENDING	ABANDONED
POWE	P OF ATTORNEY: 4	As a named inventor I	hereby appoint the	following attorney/s	) and/or amont(s) to n	rescute this application	and transact all business:
	Patent and Trademark					oscoute this application	and named an odomoso
Ds	avid J. Levy	Reg. No. 27.655	Ia	mes P. Riek	Reg. No. 39,009	Ronnie I. Dennenh	rock Reg. No. 28,209
	narles E. Dadswell	Reg. No. 35,851	V	ırgınıa C. Bennett	Reg No. 37,092		z Reg. No. 37,380
	aren L. Prus	Reg. No. 39,337		ank P Grassler	Reg No. 31,164		
	obert H. Brink izabeth Selby	Reg. No. 36,094 Reg. No. 38,298		nristopher P Rogers orie Ann Morgan	Reg. No. 36,334 Reg. No. 38,181		
		,					
	orrespondence to:		)			Direct Telephone C	Calls to:
NO.	David J. Levy, Pat		\			Kar	en L. Prus
1	Glaxo Wellcome Ir	Global Intellectual Property Department Glaxo Wellcome Inc.					-483-2192
00/	Five Moore Drive,		1				
- >	Research Triangle	Park, NC 27709					
W	Y banahar da alama	41-4-17-4-4	and the second	. C 1 1	. 1	41-4-11-4-4	
714	I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information						
	and belief are believed to be true; and further that these statements were made with t statements and the like so made are punishable by fine or imprisonment, or both, un						
34				t these statements	were made with	the knowledge that	willful false
Æ	statements and t	he like so made a	re punishable b	t these statements y fine or imprisor	were made with ment, or both, ur	the knowledge that ider 18 U.S.C. 1001	willful false
E CO	statements and t	he like so made a ements may jeopa	re punishable b	t these statements y fine or imprison ty of the applicat	were made with ment, or both, ur ion or any patent	the knowledge that ider 18 U.S.C. 1001	willful false
E CO	statements and t willful false stat	the like so made as tements may jeopa	re punishable b	t these statements y fine or imprisor ty of the applicat FIRST GIVEN NA	were made with ment, or both, ur ion or any patent	the knowledge that ider 18 U.S.C. 1001 issuing thereon.	willful false , and that such
0 +2	statements and t willful false stat FULL NAME OF INVENTOR	he like so made a ements may jeopa	re punishable b	t these statements y fine or imprison ty of the applicat	were made with ment, or both, ur ion or any patent	the knowledge that ider 18 U.S.C. 1001 issuing thereon.	willful false , and that such
	statements and t willful false stat	the like so made as tements may jeopa	re punishable b	t these statements y fine or imprisor ty of the applicat FIRST GIVEN NA	were made with ment, or both, ur ion or any patent	the knowledge that ider 18 U.S.C. 1001 issuing thereon.	willful false , and that such
04200	statements and t willful false stat FULL NAME OF INVENTOR INVENTOR'S SIGNATURE RESIDENCE &	the like so made at tements may jeopa BROWN	re punishable b	t these statements y fine or imprisor ty of the applicat FIRST GIVEN NAI Nathaniel  STATE OR FO	were made with ment, or both, ur ion or any patent	the knowledge that der 18 U.S.C. 1001 issuing thereon.  SECOND GIVEN NAM A.  COUNTRY OF CITIZE	willful false , and that such
	statements and t willful false stat FULL NAME OF INVENTOR'S INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP	the like so made attements may jeopa  FAMILY NAME BROWN  CITY Cambridge	re punishable b ardize the validi	t these statements y fine or imprisor ty of the applicat  FIRST GIVEN NAI Nathaniel  STATE OR FO MA	were made with ment, or both, ur ion or any patent	the knowledge that der 18 U.S.C. 1001 issuing thereon.  SECOND GIVEN NAM A.  COUNTRY OF CITIZE US	willful false , and that such  MEANTHAL  ENSHIP
04000	statements and t willful false stat FULL NAME OF INVENTOR INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE	rements may jeopa FAMILY NAME BROWN  CITY Cambridge POST OFFICE ADDRE	re punishable by ardize the validi	t these statements y fine or imprisor ty of the applicat  FIRST GIVENNA Nathaniel  STATE OR FO MA CITY	were made with ment, or both, un ion or any patent	the knowledge that ider 18 U.S.C. 1001 issuing thereon.  SECOND GIVEN NAM A.  COUNTRY OF CITIZE US STATE & ZIP CODER	willful false , and that such  TEANITIAL  TENSHIP  TOUNTRY
04200	statements and t willful false stat FULL NAME OF INVENTOR'S INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP	he like so made a: ements may jeopa  FAMILY NAME  BROWN  CITY  Cambridge  FOST OFFICE ADDRE  Glaxo Wellcon	re punishable by ardize the validi	t these statements y fine or imprisor ty of the applicat  FIRST GIVENNAL Nathaniel  STATE OR FC MA  City Research	were made with ment, or both, ur ion or any patent	the knowledge that der 18 U.S.C. 1001 issuing thereon.  SECOND GIVEN NAM A.  COUNTRY OF CITIZE US	willful false , and that such  TEANITIAL  TENSHIP  TOUNTRY
04000	statements and t willful false stat FULL NAME OF INVENTOR INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE	rements may jeopa FAMILY NAME BROWN  CITY Cambridge POST OFFICE ADDRE	re punishable by ardize the validi	t these statements y fine or imprisor ty of the applicat  FIRST GIVENNAL Nathaniel  STATE OR FC MA  City Research	were made with nment, or both, ur ion or any patent  ME  REIGN COUNTRY  Triangle Park	the knowledge that ider 18 U.S.C. 1001 issuing thereon.  SECOND GIVEN NAM A.  COUNTRY OF CITIZE US STATE & ZIP CODER	willful false , and that such  EENITIAL  ENSHIP
04000	statements and t willful false stat FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS FULL NAME OF INVENTOR	EMILYNAME BROWN  CITY Cambridge FOST OFFICE ADDRES Glaxo Wellcon Five Moore Dr	re punishable by ardize the validi	t these statements y fine or imprisor ty of the applicat  FIRST GIVEN NAI Nathaniel  STATE OR FO MA  CITY Research 1398	were made with ument, or both, ur ion or any patent  REIGN COUNTRY  Triangle Park  NAME	the knowledge that dder 18 U.S.C. 1001 issuing thereon.  SECOND GIVEN NAM A.  COUNTRY OF CITIZE US STATE & ZIP CODEX NC 27709, US	willful false , and that such  EENITIAL  ENSHIP
	statements and t willful false stat FULL NAME OF INVENTOR: INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS FULL NAME OF INVENTOR'S	he like so made a ements may jeope FAMILY NAME BROWN  CITY Cambridge POST OFFICE ADDRE Glaxo Wellcon Five Moore Dr FAMILY NAME CONDREAY	re punishable by ardize the validi	t these statements y fine or imprisor ty of the applicat  FIRST GIVEN NAI Nathaniel  STATE OR FO MA  CITY Research 1398	were made with ument, or both, ur ion or any patent  REIGN COUNTRY  Triangle Park  NAME	the knowledge that ider 18 U.S.C. 1001 issuing thereon.  SECOND GIVEN NAM.  A.  COUNTRY OF CITIZE US  SECOND GIVEN NAM.  NC 27709, US  SECOND GIVEN NAM.  D.	willful false , and that such  EENITIAL  ENSHIP
	statements and t willful false stat FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS FULL NAME OF INVENTOR'S SIGNATURE	ETIME TO STAND THE MENT OF T	re punishable by ardize the validi	t these statements y fine or imprisor ty of the applicat  FIRST GIVEN NAI Nathaniel  STATE OR FO MA  CITY Research 1398	were made with ument, or both, ur ion or any patent  REIGN COUNTRY  Triangle Park  NAME	the knowledge that deer 18 U.S.C. 1001 issuing thereon.  SECOND GIVEN NAM A.  COUNTRY OF CITIZE USE A 2DF CODER NC 27709, US  SECOND GIVEN NAM D.	willful false, and that such EENHAL EENHAL COUNTRY
	statements and tiviliful false stat  FULL NAME OF INVENTORS OF INVENTORS SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS  FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & RESIDENCE & RESIDENCE & RESIDENCE & RESIDENCE &	he like so made a ements may jeope BROWN  GITY  Cambridge  FOST OFFICE ADDRES  Glaxo Wellon  Five Moore Dr  FAMILY NAME  CONDREAY  TITY  THE MOORE DR  FAMILY NAME  TOTAL  THE MOORE DR  FAMILY NAME  TOTAL  THE MOORE DR  TOTAL  THE MOORE DR  FAMILY NAME  TOTAL  THE MOORE DR  THE MOORE DR  FAMILY NAME  TOTAL  THE MOORE DR  TH	re punishable by ardize the validi	t these statements y fine or imprisor ty of the applicat  FIRST GIVEN NAI Nathaniel  STATE OR FO MA  CITY Research 1398	were made with ument, or both, ur ion or any patent  REIGN COUNTRY  Triangle Park  NAME	the knowledge that ider 18 U.S.C. 1001 issuing thereon.  SECOND GIVEN NAM.  A.  COUNTRY OF CITIZE US  SECOND GIVEN NAM.  NC 27709, US  SECOND GIVEN NAM.  D.	willful false, and that such EENITAL EENITAL COUNTRY
1 2 0	statements and t willful false stat OF INVENTORS SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS FULL NAME OF INVENTORS SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE RESIDENCE & CITIZENSHIP POST OFFICE POST OFFICE	PAMILY AND PERSONNEL ADDRESS CONDREAY  CAMP TO THE ADDRESS CONDREAS CONDREAS  GRAD ADDRESS CONDREAS CONDREAS  GRAD ADDRESS CONDREAS CONDREAS  GRAD ADDRESS CONDREAS CONDREAS CONDREAS CONDREAS CONDREAS CONDREAS CONDRESS C	ss ne Inc. ive, PO Box 13	statements of the statements of the or imprison of the statements	Were made with mment, or both, ur ion or any patent  REIGN COUNTRY  Triangle Park NAME  REIGN COUNTRY	the knowledge that deer 18 U.S.C. 1001 deer 18 U.S.C. 1001 Sissuing thereon.  SECOND GIVEN NAM. A. C. STATE & A DECOME OF CHIEF O	willful false, and that such that su
	statements and twillful false stat  FULL NAME OF INVENTOR INVENTORS INVENTORS RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS FULL NAME OF INVENTOR INVENTORS INVENTORS RESIDENCE & CITIZENSHIP RESIDENCE & CITIZENSHIP	he like so made a rements may jeope mements may jeope BROWN  CITY Cambridge FOST OFFICE ADDREC GIAXO Wellcon Five Moore Dr FAMILLY NAME CONDREAY  GIR Raleigh FOST OFFICE ADDREC GIR GIAXO Wellcon	ss ne Inc.  ss ne Inc.  ive, PO Box 13	y fine or imprison y fine or imprison y fine or imprison PREST GIVEN NA Nathaniel  STATE OR FC MA CITY RESCARCH LYNN  SPATFOR FC CITY Research Research	were made with ument, or both, ur ion or any patent  REIGN COUNTRY  Triangle Park  NAME	the knowledge that deer 18 U.S.C. 1001 issuing thereon.  SECOND GIVEN NAM A.  COUNTRY OF CITIZE US STATE & 2D CODEC NC 27709, US  D.  2//3/0/COUNTRY OF CITIZE US 2//3/0/COUNTRY OF CITIZE US US	willful false, and that such that su
1 2 0	statements and t willful false stat OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP FOST OFFICE ADDRESS FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP FOST OFFICE ADDRESS	PAMILY NAME BROWN  CITY Cambridge POST OFFICE ADDRE CONDREAY  WHITE RANGE ADDRE CONDREAY  Raleigh Raleigh Glaxo Wellcon Five Moore Dr	ss ne Inc.  ss ne Inc.  ive, PO Box 13	y fine or imprisor ty of the applicat    First Given Na.     Nathaniel     STATE OR P.C.     MA.     Research     SPATOR P.C.     CITY     Research     CITY     Research     CITY     Research     CITY     Research     CITY     Research     CITY     CITY     Research     CITY     CITY     Research     CITY     CITY	I were made with union or any patent of both, union or any patent of the park	the knowledge that dder 18 U.S.C. 1001 issuing thereon.  AECONG GIVEN NAM.  COUNTRY OF CITIZE U.S.  STATE & 24F COBER NO. 27709, U.S.  STATE & 27F COBER NO. 27709, U.S.  STATE & 27F COBER NO. 27709, U.S.	willful false, and that such  EANHIAL  EOUNTRY  EOUNTRY  EOUNTRY  EOUNTRY
	statements and t willful false stat of INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP POLITION OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS	he like so made a rements may jeope mements may jeope BROWN  CITY Cambridge FOST OFFICE ADDREC GlaxO Wellcon Five Moore Dr FAMILY NAME CONDREAY  GIR GRADE GLAVE G	ss ne Inc.  ss ne Inc.  ive, PO Box 13	y fine or imprison y fine or imprison y fine or imprison PREST GIVEN NA Nathaniel  STATE OR FC MA GTY RESCAPCH LYNN  SDATFOR FC GTY RESCAPCH 1398  PRIST GIVEN NA 1398  PRIST GIVEN NA 1398	I were made with union or any patent of both, union or any patent of the park	the knowledge that deer 18 U.S.C. 1001 issuing thereon.  SECOND GIVEN NAM A.  COUNTRY OF CITIZE US  NATE A 2P CODE  NC 27709, US  3//3/O/ COUNTRY OF CITIZE US  STATE A 2P CODE  NC 27709, US  STATE A 2P CODE  NC 27709, US	willful false, and that such  EANHIAL  EOUNTRY  EOUNTRY  EOUNTRY  EOUNTRY
1	statements and t willful false stat OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP FOST OFFICE ADDRESS FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP FOST OFFICE ADDRESS	PAMILY NAME BROWN  CITY Cambridge POST OFFICE ADDRE CONDREAY  WHITE RANGE ADDRE CONDREAY  Raleigh Raleigh Glaxo Wellcon Five Moore Dr	ss ne Inc.  ss ne Inc.  ive, PO Box 13	y fine or imprisor ty of the applicat    First Given Na.     Nathaniel     STATE OR P.C.     MA.     Research     SPATOR P.C.     CITY     Research     CITY     Research     CITY     Research     CITY     Research     CITY     Research     CITY     CITY     Research     CITY     CITY     Research     CITY     CITY	I were made with union or any patent of both, union or any patent of the park	the knowledge that dder 18 U.S.C. 1001 issuing thereon.  AECONG GIVEN NAM.  COUNTRY OF CITIZE U.S.  STATE & 24F COBER NO. 27709, U.S.  STATE & 27F COBER NO. 27709, U.S.  STATE & 27F COBER NO. 27709, U.S.	willful false, and that such  EENHIAL  EOUNTRY  EOUNTRY  EOUNTRY  EOUNTRY
1 2 0 2	statements and twilfful false stat  FILL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP FOST OFFICE ADDRESS FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP FOST OFFICE ADDRESS FULL NAME OF INVENTOR'S SIGNATURE FOST OFFICE ADDRESS FULL NAME OF INVENTOR'S SIGNATURE	he like so made a ements may jeops ements may jeops BROWN  Cambridge POST OFFICE ADDRES  CONDREAY  WHILL YAME  Raleigh  Raleigh  FOST OFFICE ADDRES  GIAN Wellcon  FIVE MOORE DT  FAMILY NAME  GRAY  GRAY  GRAY  GRAY	ss ne Inc.  ss ne Inc.  ive, PO Box 13	y fine or imprisor ty of the applicat  First Given Na. Nathaniel  STATE OR FG. MA  Research 398  FIRST GIVEN LYNN  SPATOR FG. CITY Research 398  FIRST GIVEN NA. Douglas	were made with mment, or both, un identified to be the ment of the	the knowledge that deet 18 U.S.C. 1001 deet 18 U.S.C. 1001 Sissuing thereon.  SECOND GIVEN NAM. A. C. STATE & A PICODE OF STAT	willful false, and that such and that such such such such such such such such
	STATEMENT OF THE STATEM	he like so made a ements may jeope ements may jeope BROWN  GITY Cambridge FOST OFFICE ADDREC GIANO Wellcon Five Moore Dr FAMILY NAME CONDREAY  CONDREAY  FOST OFFICE ADDREC GIANO Wellcon Five Moore Dr FAMILY NAME GIANO Wellcon Five Moore Dr FAMILY NAME GRAY	ss ne Inc.  ss ne Inc.  ive, PO Box 13	FIRST GIVEN NA.  SPATFORFE.  S	were made with mment, or both, un identified to be the ment of the	the knowledge that deer 18 U.S.C. 1001 issuing thereon.  SECOND GIVEN NAM A.  COUNTRY OF CITIZE U.S.  SYATE A 2PF CODER NC 27709, U.S.  MY COUNTRY OF CITIZE U.S.  MY COUNTRY OF CITIZE U.S.  MY COUNTRY OF CITIZE U.S.  SECOND GIVEN NAM FRASE CITIZE U.S.  SECOND GIVEN NAM FRASE CITIZE U.S.  SECOND GIVEN NAM FRASE COUNTRY OF CITIZE U.S.  SECOND GIVEN NAM FRASE COUNTRY OF CITIZE U.S.	willful false, and that such and that such learning.  EASHIP  EOUNTRY  EIGENITIAL  ENSHIP  EOUNTRY  EIGENITIAL
1 2 0 2	statements and t willful false stat PILL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP FOST OFFICE ADDRESS FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP FOST OFFICE ADDRESS FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP FOST OFFICE ADDRESS FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP	he like so made a ements may jeops ements may jeops BROWN  Cambridge POST OFFICE ADDRES GIAXO Wellcon Five Moore Dr FAMILY NAME GIAXO Wellcon Five Moore Dr FAMILY NAME GRAY  CONDREAY  FIVE MOORE DR GRAY  CITY  GRAY  GRAY  CITY  GREY  GRAY  GREY  GRAY  GREY  GREY	ss ne Inc.	y fine or imprisor y fine or imprisor ty of the applicat  FIRST GIVEN NA Nathaniel  STATE OR FORE  MA  GIV  Research 398  FIRST GIVEN NA  FIRST GIVEN NA  OUR  STATE OR FORE  GIV  RESEARCH  STATE OR FORE  GIV  RESEARCH  STATE OR FORE  GIV  RESEARCH  STATE OR FORE  GB	were made with mment, or both, un identified to be the ment of the	the knowledge that deer 18 U.S.C. 1001 deer 18 U.S.C. 1001 Sissuing thereon.  SECOND GIVEN NAM. A	willful false, and that such and that such such such such such such such such
1 2 0 2	STATEMENT OF THE STATEM	he like so made a ements may jeope ements may jeope BROWN  GITY Cambridge FOST OFFICE ADDREC GIANO Wellcon Five Moore Dr FAMILY NAME CONDREAY  CONDREAY  FOST OFFICE ADDREC GIANO Wellcon Five Moore Dr FAMILY NAME GIANO Wellcon Five Moore Dr FAMILY NAME GRAY	ss ne Inc. ive, PO Box 13	FIRST GIVEN NA.  SPATFORFE.  S	were made with mment, or both, un identified to be the ment of the	the knowledge that deer 18 U.S.C. 1001 issuing thereon.  SECOND GIVEN NAM A.  COUNTRY OF CITIZE U.S.  SYATE A 2P CODE NO. COUNTRY OF CITIZE U.S.  MATE A 2P CODE NO. COUNTRY OF CITIZE U.S.  SYATE A 2P CODE NO. SECOND GIVEN NAM D.  SECOND GIVEN NAM FRASE C. 2P CODE NO. SECOND GIVEN NAM FRASE C. COUNTRY OF CITIZE U.S.  SECOND GIVEN NAM FRASE C.	willful false, and that such  EENITIAL  ENSHIP  COUNTRY  EENITIAL  ENSHIP  COUNTRY  EENITIAL  EENITIAL
1 2 2 0	statements and t willful false stat  FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP FOLL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP FOLL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP FOST OFFICE ADDRESS  FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP FOST OFFICE RESIDENCE & CITIZENSHIP FOST OFFICE RESIDENCE & CITIZENSHIP FOST OFFICE	he like so made a ements may jeope ements may jeope BROWN  GITY Cambridge FOST OFFICE ADDRES GIANO Wellcon Five Moore Dr FAMILY NAME CONDREAY  CONDREAY  FOST OFFICE ADDRES GIANO Wellcon Five Moore Dr FAMILY NAME GRAY  GRAY  GROWN  GRAY  GROWN  GRAY  GROWN  GRAY  FOST OFFICE ADDRES  GRAY  GROWN  GRAY  GROWN  G	ss and Inc. ive, PO Box 13  ss are Inc. ive, PO Box 13  ss are Inc. ive, PO Box 13	FIRST GIVEN NA.  SPATTOR FOR THE STATE OF TH	were made with mment, or both, un identified to be the ment of the	the knowledge that deer 18 U.S.C. 1001 deer 18 U.S.C. 1001 Sissuing thereon.  SECOND GIVEN NAM. A	willful false, and that such EENITIAL  ENSHIP COUNTRY  ENSHIP COUNTRY  EENITIAL  EENITIAL  EENITIAL

# COMBINED DECLARATION FOR UTILITY OF DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued

ATTORNEY'S DOCKET NUMBER
PU3514USW

I hereby claim the benefit under 35, U.S.C. §120 of any United States application or §365(c) of any PCT international application designating the United States of America that is listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, 1 acknowledge the duty lookse information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filling date of the prior application(s) and the national or PCT international filling date of this application:

PRIO	IIS PADENT	APPLICATION or PCT PAREN	T ADDI ICATO	O.V.		
111101	C.S. I ARENT	ATTECATION OF FCT FAREN	I APPLICATI	ON	OTT A TOTAL OF	
U.S.	Parent Application o	r PCT Parent Parent Fil	ing Date	DATENTEEN	STATUS (Check one)	
	Number		YYYY)	PATENTED	PENDING	ABANDONED
POWER	OF ATTORNEY:	As a named inventor, I hereby appoint the fo	llowing attorney(s)	and/or agent(c) to proce	outo this souti	
in the U.	S. Patent and Tradem	ark Office connected therewith. (List name	and registration nur	nber)	cute this application and	i transact all business
ъ.		B	-	,		
David J. Levy Reg. No. 27,655 Charles E. Dadswell Reg. No. 35,851		Reg. No. 27,655 Jame	es P. Riek	Reg. No 39,009	Bonnie L Deppenbrock Reg. No. 28,209 John L. Lemanowicz Reg. No. 37,380	
			Virginia C. Bennett Reg. No. 37,0 Frank P.Grassler Reg. No. 31,1		John L. Lemanowicz	Reg. No. 37,380
	oert H. Brink	Reg. No. 36,094 Chri	stopher P. Rogers	Reg. No. 36,334		
ASIA 2	zabeth Selby	Reg. No. 38,298 Lorie	Ann Morgan	Reg. No. 38,181		
Conde	orrespondence to					
Selly C	David J. Levy, Pat				Direct Telephone Call	ls to:
33	Global Intellectua	Property Department	2334	1.7	Karen	L. Prus
1	Glaxo Wellcome I	ne.				83-2192
146	Five Moore Drive,	PO Box 13398	PATENT TRADEM	ARK OFFICE		
flu	Research Triangle	Park, NC 27709				
N	I banabar daalaa	4-4-11-4-4				
2	and haliaf are h	that all statements made herein of	ny own knowle	age are true and tha	t all statements mad	le on information
63	and belief are be	elieved to be true; and further that the he like so made are punishable by f	iese statements	were made with the	knowledge that willful false	
(190 2100an	false statements	may jeopardize the validity of the a	me or imprisonr	nent, or both, under	r 18 U.S.C. 1001, ar	nd that such willful
791	raise statements	may jeopardize the validity of the a	ipplication or an	y patent issuing the	ereon.	
, (3	FULL NAME	FAMILY NAME	FIRST GIVEN NAM	E	SECOND GIVEN NAME/I	NITIAL
2	OF INVENTOR'S	BROWN	Nathaniel		A.	
j <sub>0</sub> 4	SIGNATURE					
0	RESIDENCE &	CITY	STATE OR FOR	EIGN COUNTRY	COUNTRY OF CITIZENS	HIP
	CITIZENSHIP	Cambridge	MA		US	
1	POST OFFICE ADDRESS	POST OFFICE ADDRESS Glaxo Wellcome Inc.	CITY		STATE & ZIP CODE/COU	NTRY
,	ADDRESS	Five Moore Drive, PO Box 1339	Research	Triangle Park	NC 27709, US	
-	FULL NAME	FAMILY NAME	FIRST GIVEN N	1345		
2	OF INVENTOR	CONDREAY	Lynn	AME	SECOND GIVEN NAME/II  D.	NITIAL
	INVENTOR'S				-	
0	SIGNATURE RESIDENCE &	CITY				
ا ن	CITIZENSHIP	Raleigh	NC.	EIGN COUNTRY	US	HIP
- 1	POST OFFICE	POST OFFICE ADDRESS	CITY		STATE & ZIP CODE/COU	NTDV
2	ADDRESS	Glaxo Wellcome Inc.	Research 7	Friangle Park	NC 27709, US	NIA!
		Five Moore Drive, PO Box 1339	8	_	,	
2	FULL NAME	FAMILY NAME GRAY	FIRST GIVEN NAME	3	SECOND GIVEN NAME/IT	NITIAL
4	OF INVENTOR'S	GRAY	Douglas		Fraser	
60	SIGNATURE	· tunter	7		\$ 16 Marc	h 2001
0	RESIDENCE &	CITY	STATE OR FOREIG	N COUNTRY	COUNTRY OF CITIZENSE	HIP
ļ	POST OFFICE	Greenford POST OFFICE ADDRESS	GB (	3 BX	GB	
3	ADDRESS	Glaxo Wellcome pic	Greenford	,	STATE & ZIP CODE/COU	
٠ ا	LEDINGOS	891-995, Greenford Road	Greentord		Middlesex UB6 0	HE, GB
- 1		, or comora Road				

## DECLARATION FOR "371" APPLICATION

		ENT APPLI	CLARATION FOR UT		ATTORNEY'S DOCKET NUMBER PU3514USW
Y	2 0 <sup>©</sup> 0	FULL NAME OF INVENTOR INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS	RUBIN  CHY Chapel Hill POST OFFICE ADDRESS Glaxo Wellcome Inc. Five Moore Drive, PO Box	STATE OR FOREIGN COUNTRY NC CITY Research Triangle Park	SECOND GIVEN NAMEZINITIAL  3 13 40 1  COUNTRY OF CITIZENSHIP  US  STATE A ZE CORDICOUNTHY  NC 27709, US
			13398		